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Indian Standard

GUIDE FOR EVALUATION OF MEDICAL DEVICES FOR BIOLOGICAL HAZARDS

PART 4 METHOD OF TEST FOR SYSTEMIC TOXICITY : ASSESSMENT OF ACUTE TOXICITY OF EXTRACTS FROM MEDICAL DEVICES

भारतीय मानक

जैव-वैज्ञानिक खतरों के लिए चिकित्सीय युक्तियों के मूल्यांकन की मार्गदर्शिका

भाग 4 सर्वदेह विषालुता की परीक्षण पद्धति : चिकित्सीय युक्तियों के निष्कर्षों की तीव्र विषालुता का मूल्यांकन

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DESCRIPTORS : MEDICAL DEVICES. BIOLOGICAL HAZARDS. SYSTEMIC TOXICITY. ACUTE TOXICITY.

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BUREAU OF INDIAN STANDARDS
MANAK BHAVAN, 9 BAHADUR SHAH ZAFAR MARG
NEW DELHI 110002

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Medical Glass Instruments and Appliances Sectional Committee, CPDC 12

FOREWORD

This Indian Standard (Part 4) was adopted by the Bureau of Indian Standards on 14 September 1988, after the draft finalized by the Medical Glass Instruments and Appliances Sectional Committee had been approved by the Consumer Products and Medical Instruments Division Council.

This part (Part 4) is one of a series of methods of test for assessing the biological hazards of the medical devices that directly contact body tissues or substances that are to be introduced into the body by means other than oral.

This standard is proposed to be published in 12 parts. Other parts are as follows:

Part 1 Terminology
Part 2 Selection of biological methods of test
Part 3 Method of testing by tissue implantation
Part 5 Method of test for intracutaneous reactivity of extracts from medical devices
Part 6 Method of test for systemic toxicity: Assessment of pyrogenicity in rabbits of extracts from medical devices
Part 7 Method of test for sensitization: Assessment of potential of medical devices to produce delayed contact dermatitis
Part 8 Methods of test for skin irritation of extracts from medical devices
Part 9 Method of test for skin irritation of solid medical devices
Part 10 Method of test for dental materials
Part 11 Method of test for eye irritation
Part 12 Method of test for toxicity to cells in culture of extracts from medical devices

Part 2 of this standard provides guidance on the selection of recommended methods of test for the initial assessment of biological hazards in medical devices which has been referred to in this part of the standard.

In the preparation of this standard, assistance has been derived from BS 5736 : Part 3 : 1981 ‘Evaluation of medical device for biological hazards : Part 3 Method of test for systemic toxicity : assessment of‘ acute toxicity of extracts’ issued by the British Standards Institution, UK.

Indian Standard

GUIDE FOR EVALUATION OF MEDICAL DEVICES FOR BIOLOGICAL HAZARDS

PART 4 METHOD OF TEST FOR SYSTEMIC TOXICITY : ASSESSMENT OF ACUTE TOXICITY OF EXTRACTS FROM MEDICAL DEVICES

1 SCOPE

1.1 This standard (Part 4) describes a method of test designed to provide information on the acute toxic effects attributable to leachable inherent or extraneous substances present in or on a medical device.

1.2 This method specifies the use of a polar and non-polar solvent to obtain extracts that are administered as a parenteral dose to mice and assessed for acute toxicity 3 to 14 days later.

1.3 This method of test is recommended for the initial assessment of devices in Category A, B_1, C and E_1 (see Part 2 of this standard):

a) *Category A* — Those intended for long-term (long-term covers a period from a few months to permanent use) implantation within the body tissue, for example, artery grafts and hip prosthesis;

b) *Category B_1* — Those intended for long-term (long-term covers a period from a few months to permanent use) or repeated contact with mucosal surfaces, for example, contraceptive devices;

c) *Category C* — Those intended for short-term (short-term covers a period from a few minutes to several weeks continuous use) use within the body or in contact with mucosal surfaces, for example, tracheal tubes, urinary catheters and intravenous cannulae;

d) *Category E_1* — Those intended to contain or administer substances including blood, that are introduced parenterally into the body, for example, blood bags, haemodialysis equipment. intravenous administration sets and kits, and hypodermic syringes.

2 DEFINITIONS

For the purpose of this standard, the following definitions shall apply.

2.1 **Acute Toxicity, Acute Toxic Effects**

Undesirable effect(s) that become apparent within an observation period of 14 days or less after administration of a single dose of extract or extractant,

2.2 **Device, Medical Device**

Any item used in medical treatment, diagnosis or contraception, not intended to have a pharmacological action on the body.

2.3 **Final Product**

Medical device in its ready-for-use state.

2.4 **Parenteral Administration**

Administration by breach of the skin or mucous surfaces.

2.5 Systemic Toxicity

Undesirable effect(s) that become apparent at sites distant from the injection site of an extract or extractant.

2.6 **Test Material**

The final product or sample of final product that is to be tested.

3 ANIMALS AND HUSBANDRY

3.1 Twelve male and twelve female albino mice of a single strain, weighing 17 to 23 g at the start of the test, shall be used.

3.2 Assign the twelve males randomly into four groups, housing three to a cage. Similarly assign the females to four separate cages.

3.3 The animals shall have free access to food and water.

4 PREPARATION OF EXTRACTS

4.1 Sterilization and Handling of Test Materials

4.1.1 Test material that is pre-sterilized (refers to devices obtained sterilized from the manufacturer or supplier) shall be handled aseptically throughout the extraction and test procedure.

4.1.2 The test material that is normally supplied non-sterile but is sterilized before use shall be sterilized before the extraction procedure and handled aseptically throughout the extraction and test procedure.

4.1.3 Test material not required to be sterile in use shall be subjected to the extraction procedure and the extracts obtained with the polar solvent shall than be sterilized before administration (*see* Note in 4.2.2)

4.2 Extractants

The following are required for preparation of extracts and for use as controls.

4.2.1 *Polar Solvent*

Sterile saline solution containing 9 g/l sodium chloride.

4.2.2 *Non-Polar Solvent*

Sesame oil or cottonseed oil conforming to II', BP or USP.

NOTE — It is recognized that it may not be practicable to sterilize the non-polar solvent. Care should be taken to minimize any possible microbiological contamination. Preparation as in 4.1.2 may be used.

4.3 Principles of Extraction

4.3.1 The test material shall be representative of the final product

4.3.1.1 To achieve this, the test material may consist of small pieces of the final product or of one or more intact devices. For large, multi-component devices, for example, dialysis units or membrane oxygenators, it may be appropriate to test the individual components of the device separately.

4.3.1.2 The quantity of any inherent or extraneous substances extracted is related to the surface area of the sample (interfacial area) with which extractant is brought into contact.

4.3.1.3 The concentration of any inherent or extraneous substances in the extract and hence the dose delivered to the animal, depends on both the interfacial area and the final extract volume.

4.3.1.4 The interfacial area per unit volume of extract has to be taken into consideration when the dose delivered to the test animal is related to the exposure of the device to patient.

4.3.2 During the extraction, the interfacial area per millilitre of final extract volume shall, where possible, be one-third of the surface area of the device that comes into direct contact either with body tissues or with mucosal surfaces and/or body fluids, or with liquids that are subsequently introduced parenterally into the body under the intended use.

NOTE -- The factor of one-third arises from consideration of the margin of safety, on the basis of an empirical dose comparison between the test animal and human. Under the conditions given in 4.3.2, the dose per kilogram of body weight administered to the test animal is approximately one thousand times greater than that which would be received from the device under intended medical use in a man weighing 70 kg.

4.3.3 The technique used in exposing the test material to the extractant shall be selected according to the requirements of 4.3.1 and 4.3.2. and may consist of total immersion or flow-through methods, or a successive extraction of more than one specimen of the final product.

4.3.3.1 Fragmentation of the test material may be used to increase the interfacial area.

4.3.4 Extraction conditions shall simulate, as nearly as possible, the conditions under which the device will normally be used.

4.3.5 During the extraction, 27 ± 3° shall be representative of room temperature and 37 ± 2° that of the body temperature.

4.3.6 The period of contact between the extractant and the test material shall be not less than 2 hours and need not be longer than 72 hours.

4.4 Procedure

4.4.1 Using the polar (4.2.1) and the non-polar solvent (4.2.2) as extractants, prepare sufficient volumes of extract of the test material in accordance with 4.1 and 4.3 to carry out the procedure described in **5.1.2.**

4.4.2 In conditions identical with those used in 4.4.1, prepare controls using both the polar solvent and the non-polar solvent, in the absence of test material.

4.4.3 Sterilize the extracts obtained with the polar solvent from unsterilized devices (*see* 4. **1.3**).

4.4.4 Record for the test report, the precise condition of extraction and, where applicable, of sterilization.

5 TEST PROCEDURE

5.1 Preparation of Animals and Administration of Extracts and extractants

5.1.1 Weigh each animal immediately before treatment and record the results for the test report.

5.1.2 Assign to each of the following four groups, one cage of three males and one cage of three females (see 3.2) and treat the groups in the manner indicated below:

a) Group *1* (*Control*) — Administer the polar solvent, 50 ml/kg, as a single intravenous injection via the lateral tail (coccygeal) vein.

b) *Group 2* (*Control*) — Administer the non-polar solvent, 50 ml/kg, as a single intraperitoneal injection.

c) *Group 3 (Test)* — Administer the extract of the test material in the polar solvent, 50 ml/kg, in the manner specified for Group 1.

d) *Group 4 (Test)* — Administer the extract of the test material in the non-polar solvent, 50 ml/kg, in the manner specified for Group 2.

5.2 Observation of Animals

5.2.1 Observe the animals frequently during 4 hours immediately following injection and at least once a day thereafter.

5.2.2 Record any signs of reaction to injection in terms of period to onset, duration and intensity.

5.2.3 Record any death and the circumstances of the death.

5.2.4 If any animals die before the end of the period of observation, perform an autopsy on decedents as described in **5.3.2**.

5.3 Termination of Test

5.3.1 Not sooner than **72** h or **later** than 14 days after the administration of extracts and extractants, weigh and kill all surviving animals and record the weights and appearances for the test report.

5.3.2 Conduct an autopsy and record the macroscopic appearance of any organs or tissues of interest, including but not restricted to, the injection site, heart, lungs, gastro-intestinal tract, liver, spleen, kidneys and gonads.

6 PRESENTATION OF RESULTS

6.1 The results shall be submitted in a test report that includes a complete record of the method of extraction and procedures followed and any other relevant data necessary for the assessment of results as described in 7.

7 ASSESSMENT OF RESULTS

7.1 The assessment of results should be carried out by an experienced person (preferably a toxicologist) who is aware of the conditions of use of the final product and has appropriate chemical **and** biological data concerning it (*see* **3.3** and 3.4 of Part 2 of this standard).

7.2 The overall assessment of test result shall be carried out taking into consideration all the information contained in the test report and, particularly any difference in the results between test groups and control groups and between sexes.

7.3 The results of the assessment **shall** be recorded in the test report.

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